

Asymmetric Total Synthesis of Pyranicin

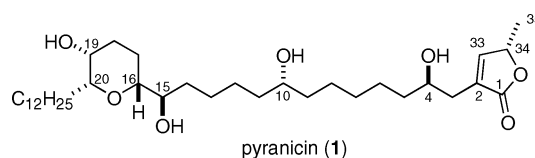
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ABSTRACT



The asymmetric total synthesis of pyranicin (1) is reported. The butenolide ring was constructed via an asymmetric alkylation/ring-closing metathesis strategy. The three stereocenters in the left-hand tetrahydropyran ring were installed by sequential chiral auxiliary-mediated aldol reactions. Closure of the tetrahydropyran and fusion of the alkyl backbone were affected via a sequential ring-closing metathesis–cross-metathesis strategy.

Pyranicin (1), a novel member of the annonaceous acetogenin family of natural products, was isolated in 1997 by McLaughlin and co-workers from the stem bark of the *Goniothalamus giganteus* tree native to Thailand.¹ Since 1982, over 400 molecules in the annonaceous acetogenin family have been identified, but pyranicin is one of only two known acetogenins to bear a tetrahydropyran (THP) ring.² These polyether natural products typically possess a terminal γ -methylbutenolide and are capped with a long hydrophobic alkyl chain. Annonaceous acetogenins are the most powerful inhibitors of mitochondrial complex I (NADH-ubiquinone oxidoreductase) in both mammalian and insect electron transport systems. It is believed that their ability to interrupt the final electron transfer from NADH to ubiquinone decreases cellular ATP production, leading to cell death by apoptosis. This unique mode of biological activity has characterized the acetogenins as promising antifeedant and pesticide treatments, as well as antimalarial, antiparasitic, and antitumor drugs, and they have recently exhibited promising results against Parkinsonism.³ Pyranicin, in particular, demonstrates selective in vitro cytotoxicity (ED₅₀ 10⁻² μ g/mL) against human pancreatic adenocarcinoma cell lines

(PACA-2).¹ Recent studies have further revealed in vivo cytotoxicity (ID₅₀ 9.4 μ M) of pyranicin against the growth of promyelocytic leukemia cells (HL-60), alternatively attributed to its ability to inhibit DNA polymerase in the cancerous cells.⁴ The interesting structures and potent biological activity have made the annonaceous acetogenins the subject of a significant amount of synthetic work.⁵ The first total synthesis of pyranicin was accomplished by Nakata and Takahashi⁶ with subsequent reports by Rein,⁷ Makabe,⁸ and Phillips.⁹

Herein, we describe an enantioselective total synthesis of pyranicin, taking advantage of chlorotitanium enolates of *N*-glycolyloxazolidinones to establish the *syn* 1,2-oxygen relationship at C15–C16 and C19–C20.¹⁰ The pyranicin

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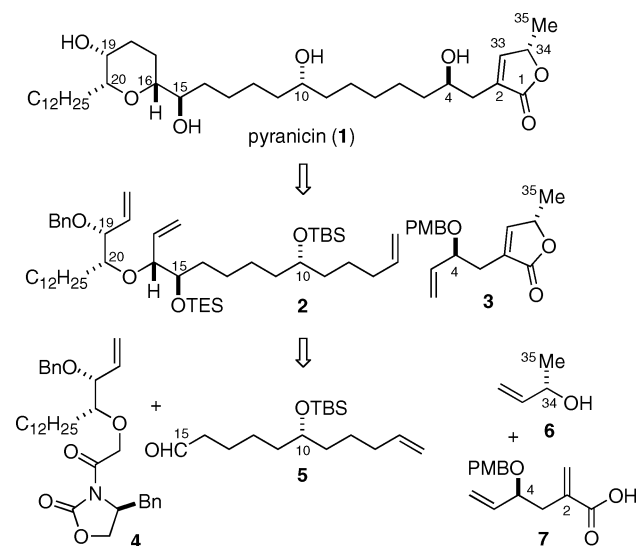


Figure 1. Original retrosynthesis of pyranicin.

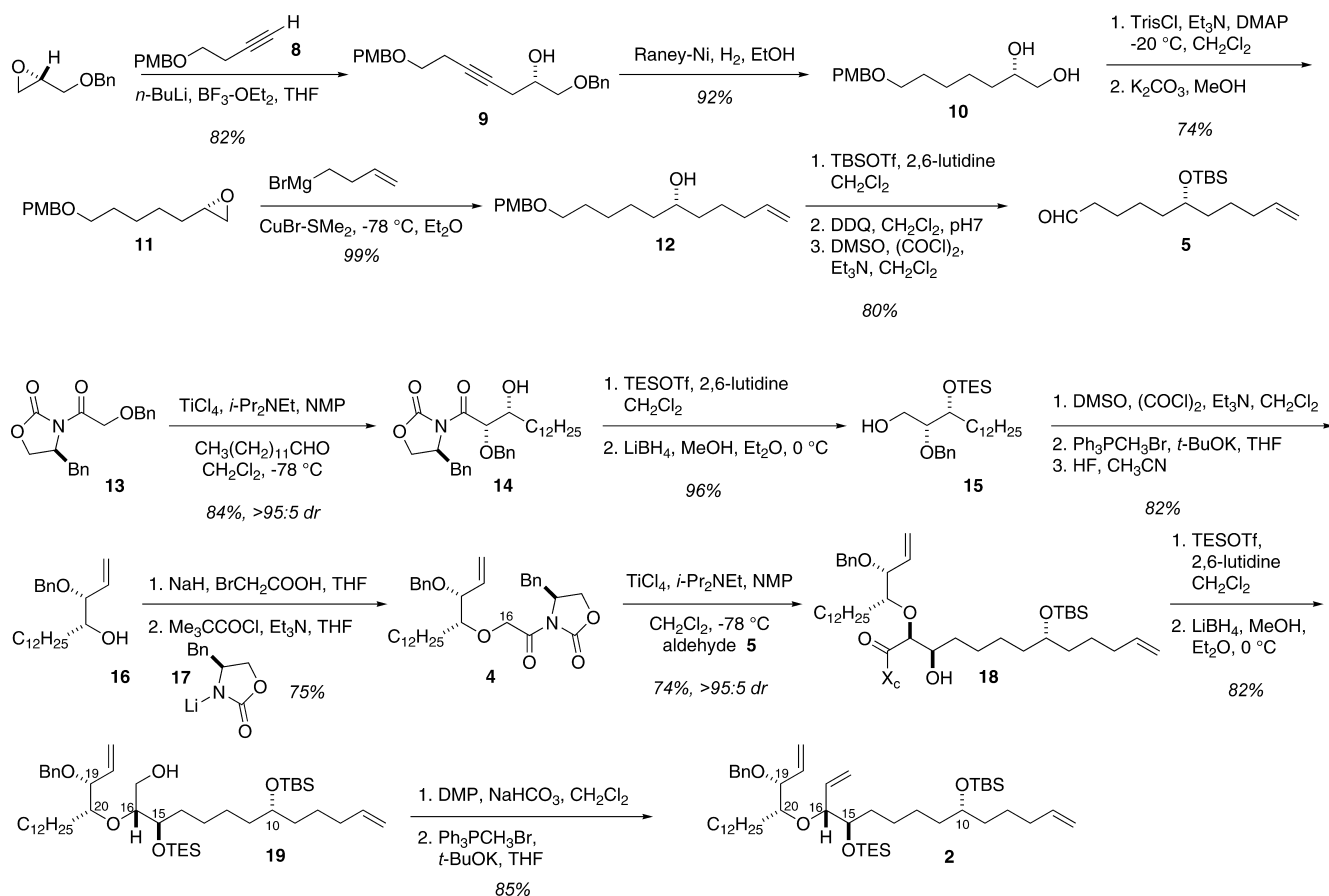
carbon backbone was envisioned to arise from a tandem ring-closing metathesis (RCM)–cross-metathesis (CM) reaction that would close the tetrahydropyran ring from triene **2** while concurrently joining the tetrahydropyran unit and butenolide

fragment **3** (Figure 1). Dihydropyran precursor **2** would be accessed via an asymmetric glycolate aldol addition of glycolyloxazolidinone **4** and aldehyde **5**. The butenolide ring would be constructed via esterification of acrylic acid **7** with (*S*)-3-buten-2-ol (**6**), followed by RCM.

Aldehyde **5** was prepared from (*S*)-benzylglycidyl ether as illustrated in Scheme 1. Lewis acid promoted addition¹¹ of lithiated homopropargyl alcohol **8** to (*S*)-benzyl glycidyl ether provided alkyne **9**. The alkyne was reduced, and removal of the benzyl group was accomplished employing Raney nickel to deliver diol **10**. Selective sulfonation of the primary alcohol was best affected employing 2,4,6-triisopropylsulfonyl chloride (TrisCl) under standard conditions whereupon treatment with base afforded epoxide **11**. Subsequently, the (*S*)-epoxide underwent copper(I)-promoted reaction with butenylmagnesium bromide to provide alcohol **12**. Ensuating alcohol protection, selective removal of the PMB ether,¹² and Swern oxidation¹³ of the primary alcohol provided the target aldehyde **5** in good yield over three steps.

Preparation of triene **2** began with a glycolate aldol reaction between benzylglycolyloxazolidinone **13** and tridecanal, providing aldol adduct **14** in good yield and excellent diastereoselectivity (Scheme 1).¹⁰ This reaction established the stereocenters at C19 and C20 at an early stage. The secondary alcohol was then protected as its triethylsilyl (TES)

Scheme 1. Preparation of Triene 2



conversion to the terminal alkene via Swern¹³ oxidation and subsequent olefination with methylenetriphenylphosphorane. Removal of the primary TBS ether followed by a two-stage oxidation yielded the corresponding acrylic acid **7**. Esterification of acid **7** with alcohol **22** was best affected via the intermediate mixed pivaloyl anhydride. Initial attempts at closure of the butenolide under standard RRCM conditions only gave the corresponding ring-opened diene **29**, presumably formed after the initial expulsion of dihydrofuran, followed by intermolecular carbene transfer. However, by sparging the reaction with argon, we were able to increase the yield of butenolide **3** from 23% to 70%, without any trace of straight-chain byproduct **29**.²⁰

The completion of the synthesis required the closure of the tetrahydropyran ring via a ring-closing metathesis and assembly of the THP and butenolide fragments through a cross-metathesis reaction (Scheme 3). Given the expected

C6 alkene of the tetrahydropyran unit, it was hoped that the two processes could be accomplished concurrently in a single exposure to a ruthenium carbene.²¹

Despite the differences in the reactivities of the two coupling fragments, however, the ensuing tandem RCM/CM reaction proved to be quite difficult to control, and suitable conditions for the tandem sequence could not be identified. The best results were found when the cross-metathesis was performed between the ring-closed monomer **30** and butenolide **3**. Therefore, it was necessary to isolate the ring-closed monomer before subjecting it to cross-metathesis with butenolide **3**. In the event, triene **2** was exposed to the Grubbs second-generation catalyst²² to close the tetrahydropyran ring. After the ring-closing metathesis product **30** was isolated in quantitative yield, the cross-metathesis between alkene **30** and butenolide **3** was achieved with the Hoveyda–Grubbs catalyst²³ in 58% yield based on recovered starting material.

Finally, exposure of triene **31** to excess tosylhydrazine and sodium acetate in aqueous dimethoxyethane at reflux,²⁴ resulted in selective hydrogenation of the C17–C18 and C5–C6 alkenes and removal of the triethylsilyl protecting group, while leaving the butenolide olefin in tact. Subjecting of the resultant butenolide to $\text{BF}_3 \cdot \text{OEt}_2$ in dimethyl sulfide provided pyranicin (**1**) in 68% yield. The synthetic sample was identical in all aspects (^1H , ^{13}C , $[\alpha]_D$) to the natural product.¹

In summary, a highly convergent total synthesis of pyranicin (**1**) has been completed. The key fragments were constructed employing asymmetric glycolate aldol and alkylation reactions followed by ring-closing metatheses; a cross-metathesis was utilized to convergently construct the backbone of the natural product.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

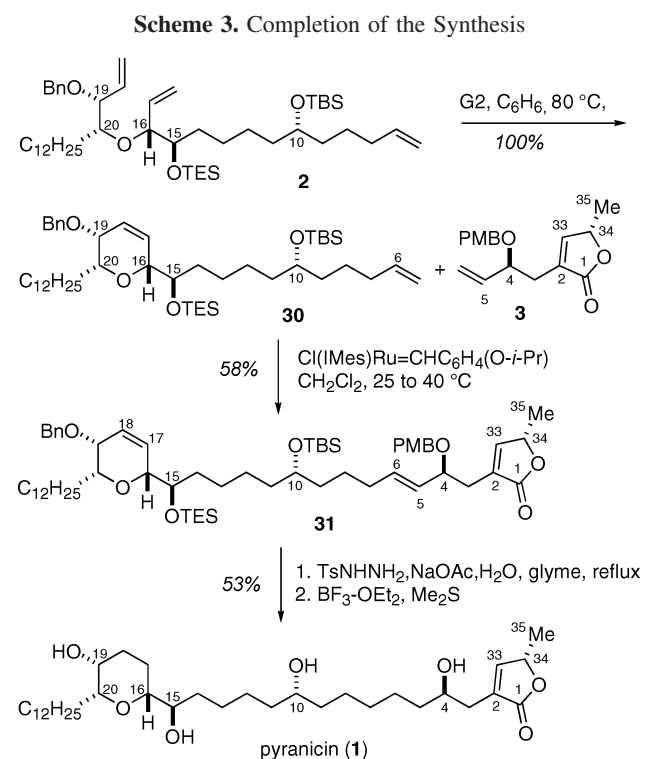
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